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## **PREVENTING DIET INDUCED DISEASE: BIOAVAILABLE NUTRIENT-RICH, LOW- ENERGY-DENSE DIETS**

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### **ABSTRACT**

What the World needs is an integrated and sustainable food policy that makes the best and most appropriate use of the technologies at our disposal to promote health and help prevent disease. Diet induced diseases account for the largest burden of chronic illnesses and health problems Worldwide. Historically a lack of knowledge about human nutritional requirements (including for the brain) helped promote diet induced disease. The scientific knowledge currently exists to help prevent many of the current deficiencies and imbalances in human diet. Primary prevention of cardiovascular disease and mental ill health starts, crucially, with maternal nutrition before the inception of pregnancy and continues throughout life of the new born and includes consuming more DHA and EPA omega-3 fats (and their cofactors) and other bioavailable brain nutrients and less high-energy-dense ( $>2$  kcal g<sup>-1</sup>) foods (e.g. land-based cereal, chocolate, alcohol and refined sugar, fat and oil), so tissues synthesize less inflammatory mediators and to lower transient short-lived meal-induced oxidative stress, inflammation, proliferation and impaired nitric oxide (e.g.  $\sim 0.35$ – $3.5$  g DHA/EPA day<sup>-1</sup> dependant on energy intake and noting the importance of cofactors). Micro- and nanotechnologies are already engineering nano foods for human (and livestock) consumption that may eventually (without excessive consumption) prevent the current diet induced disease epidemic, especially in future generations, by preventing the causal mechanisms of disease. Greater knowledge about the causal mechanisms of disease awaits to be discovered, which could further enhance the human desire to increase longevity in optimum health (creating more problems and challenges for society).

*Key words:* nanotechnology, diet, disease, cardiovascular, heart, diabetes, cancer, prevention, DHA, EPA, brain, mental, ill, health, obesity, food, pregnancy, salt, energy, nutrition

### **INTRODUCTION**

Diet (oral ingestion) has always been a major mediator of disease and

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mortality in humans e.g. malnutrition, typhoid fever and polio. Currently many of the chronic diseases epidemic in human populations are diet induced diseases. This paper attempts to provide an understanding of the magnitude of the problem of diet induced disease. The primary objective is to provide information on how to help prevent diet induced disease, including the use of food nanotechnology. Nanotechnology promises to transform medicine from being therapeutic to being preventative. It is estimated that within the next two decades human life expectancy for healthy people will approach 100 years (Tolfree and Smith 2009). This means that many people reading this paper could see the twenty-second century. Meeting people's aspirations to increase life expectancy, with all the problems it will bring to society, should be coupled with living as long as possible in good health (disease free). To achieve that future potential, it is necessary to look beyond the *status quo* e.g. medical efforts focusing more on treatments for older people than on preventing primary causes of diet induced disease before they occur – starting with appropriate maternal nutrition before the inception of pregnancy and continuing throughout the life of future generations. To understand our dietary needs it is necessary to look at human diets in relation to the causal mechanisms of disease. The review begins with the importance of diet as a fuel supply for the brain.

## NUTRITION FOR THE BRAIN

The brain evolved containing DHA (omega-3) in the sea 500–600 million years ago (Crawford *et al.*, 1999). DHA has been used in neural signalling systems over a 500–600 million year stretch of evolution. DHA is involved in neural receptor domains, gene expression with derivatives providing protection from oxidative stress in the brain and resolution of injury (Crawford *et al.*, 2008). Shellfish, fish and aquatic/shore-based animals and plants (including plankton) are the richest dietary sources of the key nutrients needed by the brain; the preformed dietary omega-3 fatty acids – DHA, EPA, iodine (I), iron (Fe), copper (Cu), zinc (Zn) and selenium (Se) (Cunnane 2005; Cunnane 2006). The omega-6 fatty acid arachidonic acid (AA) is also important for brain development and present in shellfish and other aquatic-based foods (Table I). DHA and AA are transferred across the placenta and accumulated in the brain and other organs during fetal development and maternal diet impacts fetal DHA and AA accretion (Innis, 2005; Innis, 2007). Postnatal nutrition is also a priority to ensure good maternal health and nutrition for the mother and her breast milk (Birch *et al.*, 2007). Increasing dietary alpha-linolenic acid (ALA) intake has little effect on increasing maternal transfer of DHA to the foetus, or on increasing DHA secretion in breast milk (de Groot *et al.*, 2004; Innis, 2004). Similarly, increasing the intake of ALA in infants, as in adults, has little effect on increasing circulating levels of DHA (e.g. Liou *et al.*, 2007; Ponder *et al.*, 1992).



Historically a lack of knowledge about the human nutritional requirements (including for the brain) helped promote diet induced disease. There is growing awareness that the profound environmental changes (e.g. in diet and other lifestyle conditions) that began with the introduction of agriculture and animal husbandry ~10000 years ago, occurred too recently on an evolutionary time scale for the human genome to adapt (Boaz, 2002; Eaton and Konner 1985; Eaton *et al.*, 1988; Williams and Nesse 1994). In conjunction with this discordance between our ancient, genetically determined biology and the nutritional, cultural and activity patterns in modern societies, many of the so-called diseases of civilization have emerged (Abrams, 1979; Boaz, 2002; Cohen, 1989; Cordain, 1999; Cordain *et al.*, 1998; Cordain *et al.*, 2002d; Eaton and Konner 1985; Eaton *et al.*, 1988; Frassetto *et al.*, 2001; Truswell, 1977; Williams and Nesse 1994).

#### CHRONIC DISEASE EPIDEMIC

The World spent US\$4.7 trillion on health in 2006 (World Health Organization 2009a). Chronic illnesses and health problems either wholly or partially attributable to diet account for the largest burden of chronic illnesses and health problems Worldwide. Cardiovascular diseases are the number one cause of death globally (30% of all deaths) and cardiovascular diseases are predicted to continue increasing (World Health Organization 2007). An estimated 17.5 million people died from cardiovascular diseases in 2005 (World Health Organization 2007). Cancer is a leading cause of death Worldwide and accounted for 7.9 million deaths (around 13% of all deaths) in 2007 and deaths attributable to cancer are projected to continue rising (World Health Organization 2008a). An estimated one-third of all cancer deaths are due to nutritional and life style factors (American Cancer Society 2004; Danaei *et al.*, 2005). Taking into account deaths in which diabetes was a contributory condition (heart disease or kidney failure) approximately 2.9 million deaths in 2005 were attributable to diabetes (World Health Organization 2008b). Type 2 diabetes is rapidly becoming a disease of children and adolescents. In 2000, it was estimated that 30% of boys and 40% of girls born in the USA are at risk of being diagnosed with type 2 diabetes at some point in their lives (Institute of Medicine 2005). Globally in 2005, at least 20 million children under the age of 5 years were overweight, approximately 1.6 billion adults (age 15+) were overweight and at least 400 million adults were obese (World Health Organization 2006). The World Health Organization further projects that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese. In the Europe Union, brain disorders have now overtaken all other burdens of ill health at an estimated cost of €386 billion (€829 a year for each European citizen) in 2004 (Andlin-Sobocki *et al.*, 2005) and mental ill health is predicted by the Global Forum of Health



([www.globalforumhealth.org](http://www.globalforumhealth.org)) to be in the top three burdens of ill health Worldwide by 2020.

## HUMAN DIET

There are universal characteristics of pre-agricultural hominin diets that are useful in understanding how the modern diet may predispose humans to chronic disease. Increasingly, clinical trials and interventions that use dietary treatments with nutritional characteristics similar to those found in pre-industrial and pre-agricultural diets have confirmed the beneficial health consequences predicted by the template of evolutionary discordance theory (Boaz, 2002; Cordain *et al.*, 2005; Williams and Nesse 1994).

Before the development of agriculture and animal husbandry hominin dietary choices would have been necessarily limited to minimally processed, wild foods. Agriculture, introduced novel foods as staples for which the hominin genome had little evolutionary experience. More importantly, food-processing procedures were developed, particularly following the Industrial Revolution, which allowed for quantitative and qualitative food and nutrient combinations that had not previously been encountered over the course of hominin evolution. Although refined seed (vegetable oils) and nut oils, dairy products, cereals, refined sugars, and alcohol make up 72.1% of the total daily energy consumed by all people in the USA, these types of foods would have contributed little or none of the energy in the typical pre-agricultural hominin diet (Cordain *et al.*, 2000). Additionally, mixtures of these foods make up the ubiquitous, generally energy-dense, nutrient poor, processed foods (e.g. breakfast cereals, bread, cake, cookies, crackers, cheese, fried food, pizza, pasta, kebabs, sandwiches, soft drinks, alcoholic drinks, sweets, chocolate bars, ice cream, condiments and salad dressings) that dominate the typical modern diet.

The novel foods (refined seed and nut oils, cereals, dairy products, refined sugars, fatty meats, salt, and combinations of these foods) introduced as staples during the Neolithic and Industrial Eras fundamentally altered several key nutritional characteristics of ancestral hominin diets and ultimately had far-reaching effects on health and well-being. As these foods gradually displaced the minimally processed wild foods in human diets, they adversely affected the following dietary indicators 1) fatty acid composition, 2) glycemic load, 3) macronutrient composition, 4) micronutrient density, 5) acid-base balance, 6) sodium-potassium ratio and 7) fibre content (Cordain *et al.*, 2005).

Using cereals (e.g. wheat, rice and maize) as an example, cereal grain consumption may appear to be historically remote but it is biologically recent; consequently the human immune, digestive and endocrine systems have not yet fully adapted to a food group which provides 56% of humanity's food energy and 50% of its protein (Cordain 1999). Cereal grains are truly



humanity's double-edged sword (Cordain 1999). For without them, our species would likely have never evolved the complex cultural and technological innovations which allowed our departure from the hunter-gatherer niche. However, because of the dissonance between human evolutionary nutritional requirements and the nutrient content of these domesticated grasses, many of the World's people suffer disease and dysfunction directly attributable to the consumption of cereals (Cordain 1999).

## **DIETARY FAT, EXCESS FOOD ENERGY, ESSENTIAL BRAIN NUTRIENTS AND HEALTH**

### **Dietary fat**

Substantial evidence now indicates that to prevent the risk of chronic disease, the absolute amount of dietary fat is less important than is the type of fat (Institute of Medicine of the National Academies 2002). Fatty acids fall into one of three major categories: 1) saturated fatty acids, 2) mono-unsaturated fatty acids and 3) polyunsaturated fatty acids (PUFAs). Essential PUFAs required by all mammals are not produced within the body and must come from the diet and occur in two biologically important families, omega-3 and omega-6 (Table I). The most prominent omega-6 fatty acids in the human diet are the highly unsaturated fatty acid (HUFA) AA found in aquatic foods and animal meat and the PUFA linoleic acid (LA) found in foods including seeds, nuts and their oils (Table I) which can be converted into the HUFA AA by enzymes. Existing USA and UK recommendations to increase the consumption of EPA/DHA to 1 g day<sup>-1</sup> and 0.5 g day<sup>-1</sup> for those with and without existing cardiovascular disease respectively (Kris-Etherton *et al.*, 2003; Scientific Advisory Committee on Nutrition (SACN) 2004) include consumption of shore-based foods e.g. shellfish and not just mainly pelagic oily fish e.g. mackerel and salmon (Robson 2006) and high strength DHA + EPA oils. Much of the evidence upon which these guidelines are based, however, comes from supplemented intakes of preformed DHA/EPA at levels in excess of 1 g day<sup>-1</sup> and ~3.5 g DHA/ EPA day<sup>-1</sup> has been recommended by some for current USA diets (Hibbeln *et al.*, 2006). The high requirement for DHA/EPA can likely be reduced to one-tenth of that amount by consuming less energy per meal and less energy per day (i.e. low-energy-dense food and drinks – see Table II) (compare Hibbeln *et al.* (2006) with Russo (2009)). Major dietary sources of the omega-3 PUFA ALA include seed oils (Table I), which can be converted to EPA and then DHA by enzymes. However, the conversion of ALA through to the EPA and DHA is inefficient and may be an evolutionary consequence resulting from the ubiquitous presence of DHA + EPA HUFA containing foods in the food chain of our human ancestors, thus reducing the importance of the *de novo* synthesis pathway (Damude and Kinney 2008).



TABLE I

Estimated fatty acid composition of a range of aquatic and land based foods

Food	Omeag-3 Fatty acids				Omega-6 Fatty acids	
	ALA (18:3ω-3)	EPA (20:5ω-3)	DPA <sup>2</sup> (22:5ω-3)	DHA (22:6ω-3)	LA (18:2ω-6)	AA (20:4ω-6)
g/100g						
<b>Aquatic</b>						
Mussel, blue (15164)1	0.020	0.188	0.022	0.253	0.018	0.070
Oyster, Pacific (15171)	0.032	0.438	0.020	0.250	0.032	0.038
Shrimp, mixed species (15149)	0.014	0.258	0.046	0.222	0.028	0.087
Crab, blue (15139)	0.000	0.170	0.000	0.150	0.012	0.055
Salmon, Atlantic (15076)	0.295	0.321	0.287	1.115	0.172	0.267
Mackerel, Atlantic (15046)	0.159	0.898	0.212	1.401	0.219	0.183
Catfish, channel (15010)	0.071	0.130	0.100	0.234	0.101	0.149
Seaweed, wakame (11669)	0.002	0.186	0.000	0.000	0.010	0.021
Salmon oil (04593)	1.061	13.023	2.991	13.232	1.543	0.675
<b>Land</b>						
Spinach (11457)	0.138	0.000	0.000	0.000	0.026	0.000
Kale (11233)	0.180	0.000	0.000	0.000	0.138	0.002
Carrots (11124)	0.002	0.000	0.000	0.000	0.115	0.000
Potatoes, white (11354)	0.010	0.000	0.000	0.000	0.032	0.000
Chickpeas, cooked (16057)	0.043	0.000	0.000	0.000	1.113	0.000
Mung beans, cooked (16081)	0.009	0.000	0.000	0.000	0.119	0.000
Milk, 3.7% fat (01078)	0.053	0.000	0.000	0.000	0.083	0.000
Cheese, cheddar (01009)	0.365	0.000	0.000	0.000	0.577	0.000
Butter, unsalted (01145)	0.315	0.000	0.000	0.000	2.728	0.000
Egg, whole (01123)	0.033	0.004	0.000	0.037	1.148	0.142
Chicken, with skin (05006)	0.140	0.010	0.010	0.030	2.880	0.080
Chicken, no skin (05011)	0.020	0.010	0.020	0.030	0.550	0.080
Pork, shoulder (10070)	0.130	0.000	0.000	0.000	1.600	0.100
Beef, sirloin (13954)	0.052	0.000	0.000	0.000	0.303	0.039
Lamb, domestic (17011)	0.320	0.000	0.000	0.000	1.090	0.070
Wheat flour, whole grain (20080)	0.038	0.000	0.000	0.000	0.783	0.002
Cornmeal, whole grain (20320)	0.049	0.000	0.000	0.000	1.589	0.000
Rice flour, brown (20090)	0.042	0.000	0.000	0.000	0.954	0.000
Oats (20038)	0.111	0.000	0.000	0.000	2.424	0.000
Kellogg's®, All-Bran (08001)	0.150	0.000	0.000	0.000	1.960	0.000
Kellogg's®, Corn Flakes (08020)	0.020	0.000	0.000	0.000	0.300	0.000
Kellogg's®, Special K (08067)	0.096	0.000	0.000	0.000	0.705	0.000

*Table I continues opposite*

Table 1 continued

Food	Omeag-3 Fatty acids				Omega-6 Fatty acids	
	ALA (18:3 $\omega$ -3)	EPA (20:5 $\omega$ -3)	DPA <sup>2</sup> (22:5 $\omega$ -3)	DHA (22:6 $\omega$ -3)	LA (18:2 $\omega$ -6)	AA (20:4 $\omega$ -6)
	g/100g				g/100g	
Masterfoods®, Snickers Bar (19155)	0.048	0.000	0.000	0.000	2.966	0.000
Muffins, blueberry (18274)	1.234	0.000	0.000	0.000	8.469	0.000
Bread, whole wheat (18075)	0.025	0.000	0.000	0.000	0.574	0.001
Tortillas, corn (18363)	0.034	0.000	0.000	0.000	1.385	0.000
Walnuts, english (12155)	9.080	0.000	0.000	0.000	38.093	0.000
Peanuts (16087)	0.003	0.000	0.000	0.000	15.555	0.000
Pecan nuts (12142)	0.986	0.000	0.000	0.000	20.628	0.000
Brazilnuts (12078)	0.035	0.000	0.000	0.000	20.543	0.000
Almonds (12061)	0.006	0.000	0.000	0.000	12.061	0.000
Sunflower seeds (12036)	0.060	0.014	0.000	0.000	23.050	0.000
Sesame seeds (12024)	0.363	0.000	0.000	0.000	20.654	0.000
Flaxseed (12220)	22.813	0.000	0.000	0.000	5.903	0.000
Apples, with skin (09003)	0.009	0.000	0.000	0.000	0.043	0.000
Bananas (09040)	0.027	0.000	0.000	0.000	0.046	0.000
Oranges, Florida (09203)	0.011	0.000	0.000	0.000	0.031	0.000
Olive oil (04053)	0.761	0.000	0.000	0.000	9.762	0.000
Cottonseed oil (04502)	0.200	0.000	0.000	0.000	51.500	0.100
Groundnut oil (04042)	0.000	0.000	0.000	0.000	32.000	0.000
Corn oil (04518)	1.161	0.000	0.000	0.000	53.515	0.000
Soybean oil (04044)	6.789	0.000	0.000	0.000	50.952	0.000
Sesame oil (04058)	0.300	0.000	0.000	0.000	41.300	0.000
Sunflower vegetable oil (04060)	0.200	0.000	0.000	0.000	39.800	0.000
Palm oil (04055)	0.200	0.000	0.000	0.000	9.100	0.000
Flaxseed oil (42231)	53.300	0.000	0.000	0.000	12.700	0.000
Margarine, 80% fat (04628)	2.040	0.000	0.006	0.000	22.252	0.000
Benecol®, light spread (04687)	2.187	0.000	0.000	0.000	9.724	0.000
Peanut butter (16097)	0.083	0.000	0.000	0.000	14.715	0.000

<sup>1</sup>Entries retrieved from the U.S. Department of Agriculture, Agricultural Research Service, 2007, USDA National Nutrient Database for Standard Reference, Release 20, <http://www.ars.usda.gov/ba/bhnrc/ndl> are followed by a 5-digit nutrient database number in parentheses. Data were not adjusted for country and seasonal specific differences in nutrient compositions of foods. <sup>2</sup>DPA (docosapentaenoic acid  $\omega$ -3) is an intermediary between EPA and DHA.



TABLE II

Amount (g) of a selection of foods equivalent to the 119 kcal of energy in one tablespoon (13.5 g) of olive oil (04053)

Food	g
Chocolate bar, 70–85% cocoa (19904)	20
Peanuts (16087)	21
Chocolate cookies (18159)	25
Masterfoods®, Snickers Bar (19155)	25
Muffin, blueberry (18274)	30
Cheese, cheddar (01009)	30
Oats (20038)	30
Sugars, granulated (19335)	31
Kellogg's®, Corn Flakes (08020)	33
Distilled alcoholic drink, 50% abv (14533)	41
Beef, brisket (13803)	47
Bread, whole-wheat (18075)	48
Chicken, with skin (05006)	55
Ice cream, vanilla (19095)	58
Pork, loin (10020)	60
Salmon, Atlantic (15076)	84
Anchovy, European (15001)	91
Chocolate milkshake (01110)	100
Shrimp, mixed species (15149)	112
Bananas (09040)	134
Crab, Dungeness (15143)	138
Mussel, blue (15164)	138
Red wine (14096)	140
Cod, Atlantic (15015)	145
Oyster, Pacific (15171)	147
Clam, mixed species (15157)	161
Potatoes (11354)	172
Apples (09003)	229
Seaweed, wakame (11669)	264
Orange juice, freshly squeezed (09206)	264
Carrots (11124)	290
Budweiser®, beer (14004)	290
Cola, soft drink (14148)	290
Spinach (11457)	517
Tomatoes, red (11529)	661
Lettuce (11251)	700
Drinking water, tap (14411)	N/A

<sup>1</sup>Entries retrieved from the U.S. Department of Agriculture, Agricultural Research Service, 2007, USDA National Nutrient Database for Standard Reference, Release 21, <http://www.ars.usda.gov/ba/bhnrc/ndl> are followed by a 5-digit nutrient database number in parentheses. Data were not adjusted for country and seasonal specific differences in nutrient compositions of foods.



### Heart disease

The cardio-protective effects of DHA/EPA have been recognized for over 50 years with the low incidence of mortality rate from CHD (coronary heart disease) in Greenland Eskimos, a population consuming a high fat diet, but rich in DHA/EPA (Sinclair, 1956). In Greenland, coronary heart disease is almost undetectable (Lands, 1991; Lands *et al.*, 1992), while globally cardiovascular diseases account for 30% of all deaths (World Health Organization 2007). The totality of evidence for the positive effects of DHA and EPA from aquatic food and fish oil products on various outcomes of cardiovascular disease is almost incontrovertible, according to the review by Griffin (2008). However, others state that DHA, EPA and ALA do not have a clear effect on total mortality, combined cardiovascular events, or cancer (e.g. Hooper *et al.*, 2006). The section of the Cochrane study (Hooper *et al.*, 2006) regarding cardiovascular disease has been formally rejected by the Society for the Study of Fatty Acids and Lipids (von Schacky and Harris 2007). A more recent review highlights the important cardio-protective effect of DHA/EPA in the secondary prevention of sudden cardiac death due to arrhythmias, but suggests caution to recommend dietary supplementation of PUFAs to the general population, without considering, at the individual level, the intake of total energy and fats (Russo, 2009). The current review suggests that the real value of DHA and EPA in the primary prevention of cardiovascular disease starts, crucially, with adequate maternal consumption of DHA and EPA (dependant on energy intake and noting the importance of cofactors) before the inception of pregnancy and continues with adequate intake of DHA and EPA during pregnancy and lactation and throughout the life of the new born child. The slow progressive injury to human tissues that eventually becomes cardiovascular disease and premature death becomes irreversible over time (Lands, 2005; Zieske *et al.*, 2002). Thus, secondary prevention of cardiovascular disease using DHA/EPA dietary interventions may not repair all the damage already done to human tissues by the lack of DHA and EPA and other factors in the diet earlier in life. It is important to note that if DHA and EPA fish oils undergo oxidation it may attenuate their beneficial effects (Turner *et al.*, 2006); bioactive-packaging made from nanomaterials can help to control the oxidation of food stuffs (Sozer and Kokini 2009). Further, the excessive consumption of anything may cause disease or premature death, even omega-3 (e.g. Church *et al.*, 2009; Iso *et al.*, 1989; Lichtenstein, 2005).

### Energy intake

In the USA, during the ninety year period from 1909 to 1999, a striking increase in the use of seed oils occurred. Specifically, per capita consumption of salad and cooking oils increased 130%, shortening consumption increased

136% and margarine consumption increased 410% (Gerrior and Bente 2002), which directly increased daily energy intake due to their high energy-density. Most refined fats and oils typically contain 7–9 kcal g<sup>-1</sup> (Table II). These trends occurred elsewhere in the World and were made possible by the industrialization and mechanization of the oil-seed industry (O’Keefe, 2000). The trend towards an increase in daily energy intake was exacerbated by the excessive human consumption of energy-dense cereals, seeds and nuts, and as meat from grain fed cattle, poultry and other livestock became the norm in the Western diet over the past 100 years (Cordain *et al.*, 2002d; Whitaker, 1975).

### Inflammation

The top predicted causes of death and disability Worldwide for 2020 (ischemic heart disease and unipolar major depression) and three top causes in developed regions (ischemic heart disease, cerebrovascular disease and unipolar major depression) (Murray and Lopez 1997) all seem linked to a lack of preformed DHA and EPA in the diet and excess food energy (imbalance between the intake/expenditure of energy). The close interaction between omega-3 (including DHA/EPA) and omega-6 fatty acids (including  $\gamma$ -linolenic acid (GLA, 18:3, n-6), dihomo-GLA (DGLA, 20:3, n-6) and AA) on the ability to modify inflammatory markers, production of PGI<sub>2</sub> (prostacyclin), PGE<sub>1</sub> (prostaglandin E<sub>1</sub>), PGI<sub>3</sub> (prostaglandin I<sub>3</sub>), LXs (lipoxins), resolvins (Calder 2006), neuroprotectins, NO (nitric oxide), nitrolipids, and the action of statins (HMG-CoA reductase inhibitors) and glitazones (peroxisome proliferator-activated receptors (PPARs) agonists) on essential fatty acid metabolism and NO explains the relationship between various fatty acids and CHD and stroke (Das, 2008b). Although statins were thought to block mevalonate synthesis (De Pinieux *et al.*, 1996), the hydrophilic statin Pravastatin may promote the development of cancer (inflammation) by causing an increase in mevalonate synthesis in extrahepatic tissues (Duncan *et al.*, 2005; Duncan *et al.*, 2006; Duncan *et al.*, 2007). Disease prevention is always better than treatment. Uncontrolled excessive production of pro-inflammatory mediators over prolonged periods of time is associated with heart attacks, thrombotic stroke, arrhythmia, arthritis, asthma, headaches, dysmenorrhea (menstrual cramps), inflammation, cancer and osteoporosis (Lands 1986; Samuelsson 1979) and the American Heart Association urged putting more omega-3 HUFAs into daily diets (Kris-Etherton *et al.*, 2002). However, most epidemiologic cohort studies found no association between DHA and EPA intake and cancer risk (Engeset *et al.*, 2006; MacLean *et al.*, 2006; Terry *et al.*, 2004). But, inverse associations with breast cancer have been reported in Chinese and Japanese women having omega-3 HUFA intakes up to forty times greater than Western intakes (Gago-Dominguez *et al.*, 2003; Hirose *et al.*, 2003; Wakai *et al.*, 2005). A large cohort study on



breast cancer suggested that women with the lowest DHA and EPA intake and highest omega-6 PUFA intake (highest excess food energy intake?) could benefit from increasing their omega-3 HUFA intake (Thiebaut *et al.*, 2009). It is important to note that 20–30% of dietary fatty acids undergo beta oxidation to acetyl-CoA to enter the Krebs's cycle generating the energy source adenosine triphosphate (ATP) and 15–80% are stored in adipocytes (Russo 2009). Adipose products include pro-inflammatory mediators (Ahima and Flier 2000) and excess dietary omega-6 PUFA (especially excess LA) contribute to excessive adipose tissue development (Ailhaud *et al.*, 2008). The level of AA in adipocytes (but not in phospholipid-rich tissues) has been associated with increased CHD risk (Harris *et al.*, 2007). Another study (Gago-Dominguez *et al.*, 2003) found a direct association between omega-6 PUFA intakes (highest excess food energy intake?) and breast cancer risk confined to women having the lowest intakes of omega-3 HUFAs. Such observations are consistent with the effect of the absolute amount of omega-3 fatty acids on the biosynthesis of anti-inflammatory 3-series eicosanoids (Griffin, 2008) and the negative and inflammatory effects of excess food energy intake (see above **Inflammation**); AA derived 2-series tumor promoting eicosanoids and/or decreased synthesis of anti-inflammatory and beneficial eicosanoids most likely being an underlying mechanism for cancers such as colon, breast, kidney and prostate cancer (Marmot *et al.*, 2007; Rose and Connolly 1999; Schumacher *et al.*, 2007). Tumor cells undergo apoptosis (programmed cell death) on exposure to certain fatty acids (especially in response to DHA, EPA and GLA) due to an increase in intracellular free radical generation and the formation of lipid peroxides (Das 2008b). Further studies are required to better explain the Worldwide variations in the incidence of cancer which may be linked to differences in diet and lifestyle.

### Brain nutrients

Additional evidence showed important actions of omega-3 HUFAs in brain function (Salem *et al.*, 2001). DHA is an important component of human retinal and brain membranes and has been shown to play a role in the cognitive development of infants (Iribarren *et al.*, 2004; Stoll *et al.*, 2001; Willatts and Forsyth 2000). Poor maternal health and nutrition before and during pregnancy disadvantages fetal development with permanent mental and cognitive deficits (Litt *et al.*, 2005) and behavioural dysfunction (Hibbeln *et al.*, 2007; McNamara and Carlson 2006) with a risk of heart disease, diabetes and stroke in later life – prenatal programming (Barker, 2004; Barker, 2007). Maternal nutrition before and during pregnancy is an independent risk factor for low birth weight and poor pregnancy outcome (Carlson, 2001; Doyle *et al.*, 1989; House, 2000; Rees *et al.*, 2005; Wynn *et al.*, 1994). A diet high in omega-6 PUFAs is generally thought to be associated with an increased risk of preterm delivery (Wathes *et al.*, 2007). Increasing evidence suggests that

depression, bipolar disorder, behavioral disorders and cognitive impairment in later life (dementia) also relate to a lack of DHA and EPA in the human diet (reviewed by Ruxton *et al.*, 2004). Supplementation with a combination of both DHA and EPA (or consumption of aquatic-based foods) is likely to be more effective than use of either alone (Silvers *et al.*, 2005). There is increasing evidence that the reasons for brain disorders are related to the replacement of aquatic-based foods by land-based foods (Hibbeln 2002; Hibbeln *et al.*, 2007; Hibbeln *et al.*, 2004). Thus, it is especially important to eat a diet rich in bioavailable essential brain nutrients DHA, EPA, I, Fe, Cu, Zn and Se (aquatic foods – but see **21st century solutions**) before the inception of pregnancy, during pregnancy and breastfeeding and to give it to young infants (e.g. in baby food) to ensure optimal brain development and help prevent mental ill-health. The regular consumption of essential brain nutrients should continue throughout life for reasons including: although the brain recycles its constituents rather than relying on imports, the process is not 100% efficient and the continual loss needs to be replaced by some import.

### **21st century solutions**

The growing awareness of the importance of DHA and EPA omega-3 fats is evident from the single major personal health change recommended by the health and nutrition division members of the American Oil Chemists' Society: to eat more fish and take an omega-3 supplement (American Oil Chemists' Society 2003). The fats and oils from aquatic-based foods contain high contents of these beneficial omega-3 fatty acids but increased consumer demand has also increased strain on the ability of the World's fisheries to meet demand from wild capture. Many consumers are choosing fish oil supplements or are eating foods that have been complemented with fish oils instead of consuming aquatic foods directly. However, removing undesirable odours, flavours and contaminants is expensive. In contrast, oils derived from land plants such as soybean are inexpensive and contaminant free. Given the potential benefits to the environment with regards to overfishing and the health prospects of increased consumption of these healthy fatty acids, producing these fatty acids in oilseeds is a desirable and worthy goal (but see PUFA cofactors later in **21st century solutions**). Except for the high-energy-density of fats and oils which may be reduced using nanotechnology (Farhang, 2007). Molecular biology now allows the engineering of oilseeds for the production of DHA and EPA omega-3 HUFAs in a seed oil with an omega-3:6 ratio 1.5:1 (a ratio close to that of many fish oils) (Damude *et al.*, 2008). A bread containing nanocapsules of DHA/EPA omega-3 fatty acids is being sold in Australia as Tip-Top Bread (Farhang, 2007).

Increasing human consumption of DHA and EPA omega-3 fats and by humans eating less food energy per meal (e.g. a 2000-kcal daily diet



consumed in six smaller energy portions – breakfast, brunch, lunch, afternoon tea, dinner and supper, rather than three large portions) to lower transient short-lived meal-induced oxidative stress (Libby, 2002; Ross, 1999; Stoll and Bendszus 2006), inflammation, proliferation and impaired nitric oxide (Du *et al.*, 2001; Lands, 2008; Nathan, 2008; Roberts *et al.*, 2005; Roberts *et al.*, 2002), ultimately could have far-reaching effects on health and well-being. However, appreciating the nutrients essential for brain development (Cunnane 2005; Cunnane 2006), the addition of I, Fe, Cu, Zn and Se to daily diets including DHA and EPA rich engineered seed oils with reduced levels of toxic factors and anti-nutrients (e.g. phytic acid) that impact bioavailability and utilization of nutrients and increased levels of factors that enhance bioavailability of essential nutrients (Chassy *et al.*, 2004; Gilani and Nasim 2007), would have even greater positive implications for human mental health in addition to helping prevent diet mediated inflammatory diseases. Further, for their physiological/beneficial actions PUFAs need many cofactors such as folic acid, vitamin B12, vitamin B6, vitamin C, tetrahydrobiopterin (H4B), zinc, magnesium, calcium, L-arginine, and small amounts of selenium and vitamin E (Das 2006). Hence, it is essential that these cofactors should also be provided in adequate amounts to bring about the beneficial actions of omega-3 and omega-6 fatty acids. Although principally a lack of DHA and EPA and excess food energy link diet to cardiovascular disease and premature death, evidence gleaned over the past three decades now indicates that virtually all so-called diseases of civilization arise from a complex interaction of multiple nutritional factors directly linked to the replacement of ancestral foods by the excessive consumption of novel Neolithic and Industrial era foods, along with other environmental agents and genetic susceptibility (c.f. Cordain *et al.*, 2005).

## ENERGY-DENSITY

Refined grain and sugar products nearly always maintain much higher energy densities than unprocessed fruits and vegetables. In the typical USA diet, sugars with a high energy-density (HFCS 42, HFCS 55, sucrose, glucose, honey, and syrups) now supply 18.6% of total energy, whereas refined cereal grains with a high energy-density supplies 20.4% of energy (Cordain *et al.*, 2005). Soybean oil contains 8.8 kcal g<sup>-1</sup> (data calculated from USDA National Nutrient Database for Standard Reference) and appears to deliver 20% of all calories in the median USA diet, with ~9% of all calories from LA alone (Gerrior and Bente 2002). Within the past twenty years, substantial evidence has accumulated showing that long term consumption of high-energy-dense (>2 kcal g<sup>-1</sup> (Ledikwe *et al.*, 2006)) foods can adversely affect metabolism and health (Cordain *et al.*, 2003; Liu and Willett 2002; Ludwig 2002) – see **Inflammation** and **21st century solutions** for some causal roles of excess food energy in disease. Hence, ≥39% of the total energy in the typical USA



diet is supplied by foods that may promote the causes of insulin resistance (Boden and Shulman 2002; Delprato *et al.*, 1994; McClain 2002; Rossetti *et al.*, 1990; Thomson *et al.*, 1997; Zammit *et al.*, 2001). In addition to high-energy-dense carbohydrates, other elements of Neolithic and Industrial Era foods may contribute to the insulin resistance underlying metabolic syndrome diseases. Milk, yogurt and ice cream are highly insulinotropic, with insulin indexes comparable with white bread (Ostman *et al.*, 2001). It is known that omega-3 PUFAs are of benefit in type 2 diabetes by decreasing insulin resistance (Das 2008a). Diseases of insulin resistance include obesity, type 2 diabetes and hypertension.

The global epidemic of obesity-associated diabetes is a symptom of the modern diet and lifestyle, in which food is plentiful and exercise is optional. Type 2 diabetes accounts for 90% of all diabetes cases around the World (World Health Organization 2008b). Obesity and sedentary lifestyles closely linked with this type of diabetes (World Health Organization, 2008b) are both modifiable and even preventable risk factors. A healthy diet-plus-exercise is most effective for preventing diabetes mellitus (Madden *et al.*, 2008). Unfortunately, in modern societies, it is often easier to persuade people to take a pill, than to persuade them to change their diet and lifestyle for the long-term. Diet induced metabolic syndrome may extend to other chronic illnesses and conditions that are widely prevalent in Westernized societies, including: myopia (Cordain *et al.*, 2002a), acne (Cordain *et al.*, 2002c), gout (Reaven, 1995), polycystic ovary syndrome, epithelial cell cancers (breast, colon, and prostate), male vertex balding, skin tags and acanthosis nigricans (Cordain *et al.*, 2003). Although sugars and grains with a high-energy-density now represent a dominant element of the modern urban diet, these foods were rarely or never consumed by average citizens as recently as two hundred years ago (Cordain *et al.*, 2005). Diseases of insulin resistance are rare or absent in hunter-gatherer and other less westernized societies living and eating in their traditional manner (Eaton *et al.*, 1988; Schaefer, 1971; Trowell, 1980).

The finding that persons with a low-energy-dense ( $<1.6$  kcal g<sup>-1</sup>) diet had the lowest total intakes of energy, even though they consumed the greatest amount of food has important implications for promoting compliance with prescribed diets (Ledikwe *et al.*, 2006). A reduction in liquid calorie intake has been found to have a stronger effect than has a reduction in solid calorie intake on weight loss (Chen *et al.*, 2009). Of the individual beverages, only intake of sugar-sweetened beverages (SSBs) was significantly associated with weight change in the study by Chen *et al.* (2009). A diet plan that severely restricts the amount of food a patient consumes will likely lead to feelings of hunger and have unfavourable influences on the patient's satisfaction with the diet and long-term compliance. Overweight and obese patients may develop paradoxical nutritional deficiency from eating high-energy foods with a poor nutrient content. The impact of sedentary lifestyles and availability of energy-dense food in modern societies is undeniable, but



substantial individual differences in body weight persist, suggesting that individuals respond differently to the ‘obesogenic’ environment (Carnell and Wardle 2008). Psychometric measures of child appetite and child weight suggest that appetitive trait profiles may not only promote obesity but also protect against it and will include both genetic and environmental influences (Carnell and Wardle 2008) which require further investigation.

High energy-density (c.f. Table II) and low nutrient density (Table III and see **MICRONUTRIENT DENSITY**) which characterise diet in developed countries are major targets that must be overcome. 2000 kcal day<sup>-1</sup> = 334 g of chocolate (70–85% cocoa) (19904), 353 g peanuts (16087), 496 g cheddar cheese (01009), 554 g Kellogg’s® Corn Flakes (08020), 678 g alcoholic drink 50% abv (14533), 752 g white bread (18069), 2326 g mussel meat (15164), 2439 g cod (15015), 4444 g fresh orange juice (09206) or 8695 g spinach (11457) (data calculated from USDA National Nutrient Database for Standard Reference are followed by a 5-digit nutrient database number in parentheses). Nanotechnology or molecular biology may be able to engineer high-energy-dense foods abundant in the modern diet to maintain lower energy densities (<1.6 kcal g<sup>-1</sup>) while looking and tasting the same as before modification to aid public acceptance and reduce any insulinotropic properties with potential positive effects on metabolism and health. Ultrafine food technology (Eminate Limited, Nottingham, UK) has produced food products that improve the impact on taste sensation per mouthful, enabling the manufacturers of processed foods to reduce their energy-density and therefore create a healthier product (see also Farhang, 2007).

## MACRONUTRIENT COMPOSITION

In the present USA diet, the percentage of total food energy derived from the three major macronutrients is as follows: carbohydrate (51.8%), fat (32.8%), and protein (15.4%) (Cordain *et al.*, 2005). Advice for reducing the risk of cardiovascular disease and other chronic diseases has been to limit fat intake to 30% of total energy, to maintain protein at 15% of total energy and to increase complex carbohydrates to 55–60% of total energy (e.g. Krauss *et al.*, 2000). Both the current USA macronutrient intakes and suggested healthful levels differ considerably from average levels obtained from ethnographic (Cordain *et al.*, 2000) and quantitative (Cordain *et al.*, 2002b) studies of hunter gatherers in which dietary protein is characteristically elevated (19–35% of energy) at the expense of carbohydrate (22–40% of energy) (Cordain *et al.*, 2002b; Cordain *et al.*, 2000). Because protein has > three times the thermic effect of either fat or carbohydrate (Croveti *et al.*, 1998) and because it has a greater satiety value than fat or carbohydrate (Croveti *et al.*, 1998; Stubbs 1998), increased dietary protein may represent an effective weight-loss strategy for the overweight or obese. Studies have indicated that fish protein may have a greater effect on satiety compared to other protein



TABLE III

Examples of the estimated vitamin and mineral content of refined and unrefined sugar, a seed oil, shellfish, land-based meat, a vegetable and a fruit

Food									
	Units/ 100g	Sucrose <sup>1,2</sup> (19335)	Molasses <sup>3</sup> (19304)	Sunflower oil (04060)	Mussel, blue (15164)	Oyster, Pacific (15171)	Beef, grass fed (13047)	Broccoli (11090)	Apples, with skin (09003)
Vitamin C	mg	0	0	0	8.0	8.0	0	89.2	4.6
Vitamin B-12	µg	0	0	0	12.00	16.00	1.97	0	0
Niacin	mg	0	0.930	0	1.6	2.010	4.818	0.639	0.091
Riboflavin	mg	0.019	0.002	0	0.210	0.233	0.154	0.117	0.026
Thiamine	mg	0	0.041	0	0.160	0.067	0.049	0.071	0.017
Folate	µg	0	0	0	42	10	6	63	3
Vitamin B-6	mg	0	0.670	0	0.050	0.050	0.355	0.175	0.041
Vitamin A	µg <sup>4</sup>	0	0	0	48	81	0	31	3
Calcium	mg	1	205	0	26	8	12	47	6
Iron	mg	0.01	4.72	0.03	3.95	5.11	1.99	0.73	0.12
Magnesium	mg	0	242	0	34	22	19	21	5
Phosphorous	mg	0	31	0	197	162	175	66	11
Potassium	mg	2	1464	0	320	168	289	316	107
Sodium	mg	0	37	0	286	106	68	33	1
Zinc	mg	0	0.29	0	1.60	16.62	4.55	0.41	0.04
Copper	mg	0	0.487	NA	0.094	1.576	0.063	0.049	0.027
Manganese	mg	0	1.530	NA	3.400	0.634	0.010	0.210	0.035
Selenium	µg	0.6	17.8	NA	44.8	77.0	14.2	2.5	0.0

<sup>1</sup>Entries retrieved from the U.S. Department of Agriculture, Agricultural Research Service, 2007, USDA National Nutrient Database for Standard Reference, Release 20, <http://www.ars.usda.gov/ba/bhnr/hdl> are followed by a 5-digit nutrient database number in parentheses. Data were not adjusted for country and seasonal specific differences in nutrient compositions of foods. <sup>2</sup>Sucrose is a refined sugar. <sup>3</sup>Molasses is unrefined sugar. <sup>4</sup>Vitamin A units in retinol activity equivalents (RAE).



sources of animal origin (see Borzoei *et al.*, 2006). Clinical trials have shown that calorie-restricted, high-protein diets are more effective than calorie-restricted, high-carbohydrate diets in promoting (Baba *et al.*, 1999; Layman 2003; Skov *et al.*, 1999) and maintaining (Westerterp-Plantenga *et al.*, 2004) weight loss in overweight subjects while producing less hunger and more satisfaction (Johnston *et al.*, 2004). Furthermore, high protein diets have been shown to improve metabolic control in patients with type 2 diabetes (Odea 1984; Odea *et al.*, 1989; Seino *et al.*, 1983). In obese women, hypocaloric, high-protein diets improved insulin sensitivity and prevented muscle loss, whereas hypocaloric, high-carbohydrate diets worsened insulin sensitivity and caused reductions in fat free mass (Piatti *et al.*, 1994). In numerous population studies, summarized by Obarzanek *et al.* (1996), higher blood pressure has been associated with lower intakes of protein. An increasing body of evidence indicates that high-protein diets may improve blood lipid profiles (Odea 1984; Odea *et al.*, 1989; Wolfe and Giovannetti 1991; Wolfe and Giovannetti 1992; Wolfe and Piche 1999) and thereby lessen the risk of diet induced disease.

Improvements in the nutritional value of crop plants, in particular the protein composition has been a major long-term goal of plant breeding programs. Molecular biology has produced transgenic potatoes with about 33% more protein and substantial amounts of essential amino acids including lysine (Chakraborty *et al.*, 2000), which is deficient in many developing countries where diets are heavily based on cereals (Cordain 1999; Gilani and Nassim 2007). Strains of protein-enriched maize have also been created (Glenn 2007). Some protein based nanotubes are considered food-grade materials (Graveland-Bikker and De Kruif 2006), which should make their introduction into the human food chain relatively easy and might further facilitate increases in protein composition of currently high carbohydrate foods. The future looks promising to increase protein consumption at the expense of carbohydrate in the human diet, with potential health benefits.

#### MICRONUTRIENT DENSITY

Refined sugars are essentially devoid of any vitamin or mineral (Table III). Accordingly, the consumption of refined sugar or foods containing refined sugar reduces the total vitamin and mineral (micronutrient) density of the diet by displacing more nutrient dense foods (Table III). A similar situation exists for refined seed and nut oils (Table III), except that they contain two fat-soluble vitamins (vitamin E and vitamin K) (First Data Bank 2000). Because seed and nut oils and refined sugars contribute  $\geq 36.2\%$  of the energy in a typical USA diet, the widespread consumption of these substances, or foods made with them, has considerable potential to influence the risk of vitamin and mineral deficiencies (Cordain *et al.*, 2005). At least half the USA population fails to meet the recommended dietary allowance (RDA)

for vitamin B-6, vitamin A, magnesium, calcium, and zinc, and 33% of the population does not meet the RDA for folate (Cordain *et al.*, 2005). Wild foods known to be consumed by hunter-gatherers generally maintain higher micronutrient concentrations than do their domesticated counterparts (Brand-Miller *et al.*, 1998; Eaton and Konner 1985), including the muscle meat of wild animals (First Data Bank 2000).

Endemic clinical and sub-clinical iodine deficiency is present in about 20% of humans Worldwide. The global problem of iodine deficiency primarily affects people not regularly consuming shellfish, fish or iodized table salt (but see **SALT**), without which clinical hypothyroidism, subnormal cognitive development and cretinism would still be the public health dilemma they were prior to iodization of table salt (Cunnane *et al.*, 2007). The scale and impact of endemic iodine deficiency is rivalled only by iron deficiency. Two billion people, over 30% of the World's population are anaemic, many due to lack of iron (World Health Organization 2009b). Unlike iodine, iron is not yet legislated into the food supply but great efforts are being made to find a simple, cheap, reliable way to provide iron supplements where they are needed. Iron and other key minerals needed for brain development and function (zinc, copper, selenium) are more bioavailable from shellfish and fish than from plant-based diets where their absorption is impaired by phytates and other anti-nutrients. Plant based diets rich in staples like cassava or soy (the basis of many vegan and vegetarian food products) are not only a very poor source of iodine but they also contain goiterogens which inhibit iodine absorption (Cunnane *et al.*, 2007).

The displacement of more nutrient-dense foods (e.g. aquatic-based foods) by less nutrient-dense novel foods (refined sugars, cereals, seed and nut oils and dairy products) and the subsequent decline in dietary vitamin and mineral density has far reaching health implications, consequences that not only promote the development of vitamin-deficiency diseases but also numerous infectious and chronic diseases (Cordain 1999).

Biofortification of novel foods through modern methods of biotechnology/nanotechnology has the potential to help offset essential nutrient deficiencies and improve human health through elevated levels of essential nutrients (including their cofactors (Das 2006)), reduced levels of toxic factors and anti-nutrients that impact bioavailability and utilization of nutrients, and increased levels of factors that enhance bioavailability of nutrients (Chassy *et al.*, 2004; Gilani and Nasim 2007). A number of crops, developed with a focus on improving nutritional quality are advancing through regulatory processes towards commercialization (Gilani and Nasim 2007). Some examples of nutritionally enhanced crops include cyanogen-free cassava (Siritunga and Sayre 2003); nutritionally enhanced rice with an elevated level of beta-carotene (Paine *et al.*, 2005), increased levels of iron and zinc (Vasconcelos *et al.*, 2003), an elevated level of cysteine residues to enhance iron bioavailability and a decreased level of phytates to improve iron and zinc bioavailability (Lucca *et al.*, 2002); and tomatoes and soybeans with



increased antioxidant contents (World Health Organization 2005b). Food and nutrition products that contain nanoscale additives are already being sold, such as iron in nutritional drink mixes, micelles that carry vitamins, minerals and phytochemicals in oil and zinc oxide in breakfast cereals (Sozer and Kokini 2009). Other food nanotechnology products are cooking oils that contain nutraceuticals within nanocapsules and nanoparticles that have the ability to selectively bind and remove chemicals from food ('Nanotechnology in agriculture and food', available at <http://www.nanoforum.org>). Delivery of fragile micronutrients including their cofactors can be improved through nanoencapsulation (Sorrentino *et al.*, 2007). By reducing particle size, nanotechnology can contribute to improve the properties of bioactive compounds (e.g. DHA and EPA), such as delivery properties, solubility, prolonged residence time in the gastrointestinal tract and efficient absorption through cells (Chen *et al.*, 2006). Bioactive compounds that are encapsulated into the packaging itself are a promising approach because this would allow the release of the active compounds in a controllable manner (Sozer and Kokini 2009).

#### ACID-BASE BALANCE

After digestion, absorption, and metabolism, nearly all foods release either acid or bicarbonate (base) into the systemic circulation (Frassetto *et al.*, 1998; Sebastian *et al.*, 2002). Virtually all pre-agricultural diets were net base yielding because of the absence of cereals and energy-dense, nutrient poor foods, foods that were introduced during the Neolithic and Industrial Eras and that displaced base-yielding fruit and vegetables (Sebastian *et al.*, 2002). Consequently, a net base-producing diet was probably the norm throughout most of hominin evolution (Sebastian *et al.*, 2002). The known health benefits of a net base-yielding diet include preventing and treating osteoporosis (Bushinsky 1996; Sebastian *et al.*, 1994), age-related muscle wasting (Frassetto *et al.*, 1997), calcium kidney stones (Pak *et al.*, 1985; Preminger *et al.*, 1985), hypertension (Morris *et al.*, 1999; Sharma *et al.*, 1990), and exercise-induced asthma (Mickleborough *et al.*, 2001) and slow the progression of age and disease-related chronic renal insufficiency (Alpern and Sakhaee 1997). Research is required to determine if micro- and nanotechnologies can modify novel net acid producing cereals to become net base yielding foods.

#### SALT

The average sodium content (3436 mg day<sup>-1</sup>) of the typical USA diet is substantially higher than its potassium content (2617 mg day<sup>-1</sup>) (U.S. Department of Agriculture 2008). The addition of manufactured salt to the

TABLE IV

Estimated sodium and potassium composition of a range of foods available in most developed countries

Food	Sodium mg/100g	Potassium mg/100g
Salt, table (02047) <sup>1</sup>	38758	8
Shrimp, mixed species (15149)	148	185
Salmon, chinook (15078)	47	394
Salmon, chinook smoked (15179)*	2000	175
Spinach (11457)	79	558
Bananas (09040)	1	358
Wheat flour, whole-grain (20080)	5	405
Bread, whole-wheat (18075)*	472	248
Milk, 3.7% fat (01078)	49	151
Cheese, cheddar (01009)*	621	98
Butter, unsalted (01145)	11	24
Butter, salted (01001)*	576	24
Pork, shoulder (10070)	65	302
Pork, salami (07071)*	2260	378
Kellogg's®, Corn Fakes (08020)*	723	79
Kellogg's®, Special K (08067)*	721	196
Masterfoods®, Milky Way Bar (19135)*	167	124
Margarine, 80% Fat (04628)*	654	18
Benecol®, light spread (04687)*	670	4
Soy sauce (16123)*	5637	217
Peanuts, dry roasted (16390)	6	658
Peanuts, dry roasted (16090)*	813	658

<sup>1</sup>Entries retrieved from the U.S. Department of Agriculture, Agricultural Research Service, 2007, USDA National Nutrient Database for Standard Reference, Release 20, <http://www.ars.usda.gov/ba/bhnrc/ndl> are followed by a 5-digit nutrient database number in parentheses. Data were not adjusted for country and seasonal specific differences in nutrient compositions of foods. \*indicates the addition of sodium salt to the food.

food supply and the displacement of traditional potassium-rich foods by foods introduced during the Neolithic and Industrial periods (Tables III and IV) caused a 400% decline in the potassium intake while simultaneously initiating a 400% increase in sodium ingestion (Cordain 2002; Eaton and Konner 1985; Frassetto *et al.*, 2001). The potassium concentrations in vegetables are four and twelve times those in milk and whole grains respectively, whereas in fruit the potassium concentration is two and five times that in milk and whole grains (First Data Bank 2000). The inversion of potassium and sodium concentrations in hominin diets had no evolutionary precedent and now plays an integral role in eliciting and contributing to numerous diseases of civilization (Cordain *et al.*, 2005). Diets low in potassium and high in sodium may partially or directly underlie or exacerbate a variety of maladies and chronic illnesses, including hypertension, stroke, kidney stones,



osteoporosis, gastrointestinal tract cancers, asthma, exercise-induced asthma, insomnia, air sickness, high-altitude sickness and Meniere's Syndrome (ear ringing) (Antonios and MacGregor 1996; Carey *et al.*, 1993; Devine *et al.*, 1995; Gotshall *et al.*, 2000; Jansson 1986; Lindseth and Lindseth 1995; Massey and Whiting 1995; Miller 1945; Porcelli and Gugelchuk 1995; Thai-Van *et al.*, 2001; Tuyns 1988).

The more sodium chloride (NaCl) salt one uses the more one needs it in all kind of foods (e.g., bread, potatoes, cheese, etc) due to the damaging effect of NaCl salt on taste-buds, which may be irreversible in older people, but is normally recoverable within a couple of months on a low NaCl salt diet (Joossens *et al.*, 1981). Simply not adding NaCl salt to (processed) food and the biofortification of cereals and dairy products with potassium may help alleviate the current sodium-potassium imbalance in the human diet. However, there is evidence that NaCl, rather than Na per se, is responsible for the known adverse effects of dietary salt on health (McCarty 2004)

## FIBRE CONTENT

The fibre content ( $15.1 \text{ g day}^{-1}$ ) (U.S. Department of Agriculture 2008) of the typical USA diet is considerably lower than some recommended values (25–30 g) (Krauss *et al.*, 2000). Refined sugars, seed and nut oils, dairy products, and alcohol are devoid of fibre and constitute an average of 48.2% of the energy in the typical USA diet (Cordain *et al.*, 2005). Furthermore, fibre-depleted, refined grains represent 85% of the grains consumed in the USA and because refined grains contain 400% less fibre than whole grains (by energy), they further dilute the total dietary fibre intake (Cordain *et al.*, 2005). Fresh fruit typically contains twice the amount of fibre in whole grains, and non starchy vegetables contain almost eight times the amount of fibre in whole grains on an energy basis (First Data Bank 2000). Fruit and vegetables known to be consumed by hunter-gatherers also maintain considerably more fibre than do their domestic counterparts (Brand-Miller *et al.*, 1998). Diets low in dietary fibre may underlie or exacerbate constipation, appendicitis, hemorrhoids, deep vein thrombosis, varicose veins, diverticulitis, hiatal hernia and gastroesophageal reflux (Trowell, 1985).

Fibre type and quantity are undoubtedly under genetic control, although this topic has received little attention. The technology to modify fibre content and type by micro- and nano-engineering would be a great benefit in persuading the many individuals who, for taste or other reasons, do not include adequate amounts of fibre in their daily diet. For example, fibre content could be added to more preferred foods e.g. milk, cheese, ice cream, refined cereals and white bread – but these are all novel foods that can currently (without modification) promote the diet induced diseases of civilization.



## SCIENCE COMMUNICATION TO THE PUBLIC

The risks of well regulated and rigorously tested food micro- and nanotechnology products that help prevent disease are likely to be insignificant when compared with the magnitude of the current problem of the diet induced disease epidemic. Using nanotechnology (or molecular biology) to engineer foods so they cannot (without excessive consumption) promote diet induced disease is likely to be of great benefit to mankind. In reality there are already more humans on Earth, than can be sustained by the natural World. However, the consumption of (wild) aquatic-based foods e.g. omnivorous shellfish in a sustainable manner (Robson 2006) should be encouraged and nanotechnology will probably enhance the production, utilization and food safety of this nutritious resource. Nanotechnology will change society beyond anything that has gone before. This should, but not with any certainty, eventually slow down the spiraling diet induced healthcare costs. Further, today's controversial areas such as nanotechnologies in foods, stem cell research, cloning, gene therapy, human enhancement and biochip implants will become acceptable practice before 2050 (Tolfree and Smith 2009).

## CONCLUSION

Chronic illnesses and health problems either wholly or partially attributable to diet account for the largest burden of chronic illnesses and health problems Worldwide. These diseases (e.g. cardiovascular disease) are epidemic in modern societies and typically afflict 50–65% of the adult population, yet they are rare or non-existent in hunter-gatherers and other less Westernized people. What the World needs is an integrated and sustainable food policy that makes the best and most appropriate use of the technologies at our disposal. To promote health and help prevent disease the future direction of food production should be towards greater production of anti-inflammatory (DHA, EPA, ALA, LA and AA profile similar to aquatic foods e.g. mussels *Mytilus spp.*), higher protein (~ one third of total food energy intake at the expense of lowered carbohydrate), low-energy-dense i.e. high water content ( $<1.6 \text{ kcal g}^{-1}$ ), high fibre ( $25\text{--}30 \text{ g day}^{-1}$ ), high potassium – low sodium chloride, bioavailable nutrient-rich (including cofactors) brain foods (foods rich in preformed DHA, EPA, I, Fe, Cu, Zn and Se – aquatic foods, nano foods?). Micro- and nanotechnologies are already engineering nano foods for human (and livestock) consumption that may eventually (without excessive consumption) prevent the current diet induced disease epidemic, especially in future generations, by preventing the causal mechanisms of disease. Nanoscience and nanotechnology are new frontiers and their potential cannot be underestimated. There is still a substantial amount of knowledge about the causal mechanisms of disease that awaits to be discovered, which could





further enhance the human desire to increase longevity in optimum health (creating more problems and challenges for society).

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## REFERENCES

- Abrams, H.L. (1979). The relevance of paleolithic diet in determining contemporary nutritional needs. *J Appl Nutr*, **31**, 43–59.
- Ahima, R.S., Flier, J.S. (2000). Adipose tissue as an endocrine organ. *Trends Endocrinol Metab.*, **11**, 327–332.
- Ailhaud, G., Guesnet, P., Cunnane, S.C. (2008). An emerging risk factor for obesity: does disequilibrium of polyunsaturated fatty acid metabolism contribute to excessive adipose tissue development? *Br J Nutr.*, **100**, 461–470.
- Alpern, R.J., Sakhaee, K. (1997). The clinical spectrum of chronic metabolic acidosis: Homeostatic mechanisms produce significant morbidity. *Am J Kidney Dis.*, **29**, 291–302.
- American Cancer Society (2004). *Cancer facts & figures 2004*. American Cancer Society Atlanta.
- American Oil Chemists' Society (2003). What the experts eat: the health and nutrition division weighs in with nutrition advice. *Inform (American Oil Chemists' Society)*, **14**, 116–117.
- Andlin-Sobocki, P., Jonsson, J., Wittchen, H.-U., Olesen, J. (2005). Cost of disorders of the brain in Europe. *Eur J Neurol.*, **12**, 1–27.
- Antonios, T.F.T., MacGregor, G.A. (1996). Salt – More adverse effects. *Lancet*, **348**, 250–251.
- Baba, N.H., Sawaya, S., Torbay, N., Habbal, Z., Azar, S., Hashim, S.A. (1999). High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. *Int J Obes.*, **23**, 1202–1206.
- Barker, D.J. (2004). The developmental origins of chronic adult disease. *Acta Paediatr.*, **93**, 26–33.
- Barker, D.J. (2007). The origins of the developmental origins theory. *J Intern Med.*, **61**, 412–417.
- Birch, E.E., Garfield, S., Castaneda, Y., Hughbanks-Wheaton, D., Uauy, R., Hoffman, D. (2007). Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula. *Early Hum Dev.*, **83**, 279–284.
- Boaz, N.T. (2002). *Evolving health: the origins of illness and how the modern world is making us sick*. Wiley & Sons, Inc; New York.
- Boden, G., Shulman, G.I. (2002). Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. *Eur J Clin Investig.*, **32**, 14–23.



- Borzoei, S., Neovius, M., Barkeling, B., Teixeira-Pinto, A., Rossner, S. (2006). A comparison of effects of fish and beef protein on satiety in normal weight men. *Eur J Clin Nutr.*, **60**, 897–902.
- Brand-Miller, J.C., Holt, S.H.A. (1998). Australian Aboriginal plant foods: a consideration of their nutritional composition and health implications. *Nutr Res Rev.*, **11**, 5–23.
- Bushinsky, D.A. (1996). Metabolic alkalosis decreases bone calcium efflux by suppressing osteoclasts and stimulating osteoblasts. *Am J Physiol Renal Physiol.*, **271**, F216–F222.
- Calder, P.C. (2006). n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr.*, **83**, 1505S–1519S.
- Carey, O.J., Locke, C., Cookson, J.B. (1993). Effect of alterations of dietary-sodium on the severity of asthma in men. *Thorax*, **48**, 714–718.
- Carlson, S.E. (2001). Docosahexaenoic acid and arachidonic acid in infant development. *Semin Neonatol*, **6**, 437–449.
- Carnell, S., Wardle, J. (2008). Appetitive traits and child obesity: measurement, origins and implications for intervention. *Proc Nutr Soc.*, **67**, 343–355.
- Chakraborty, S., Chakraborty, N., Datta, A. (2000). Increased nutritive value of transgenic potato by expressing a nonallergenic seed albumin gene from *Amaranthus hypochondriacus*. *Proc Natl Acad Sci USA*, **97**, 3724–3729.
- Chassy, B.M., Hlywka, J.J., Kleter, G.A., Kok, E.J., Kuiper, H.A., McGloughlin, M., Munro, I.C., Phipps, R.H., Reid, J.E. (2004). Nutritional and safety assessments of foods and feeds nutritionally improved through biotechnology. *Comp. Rev. Food Sci. Food Safety*, **3**, 35–104.
- Chen, L., Appel, L.J., Loria, C., Lin, P.H., Champagne, C.M., Elmer, P.J., Ard, J.D., Mitchell, D., Batch, B.C., Svetkey, L.P. (2009). Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER trial. *Am J Clin Nutr.*, doi:10.3945/ajcn.2008.27240.
- Chen, L., Remondetto, G.E., Subirade, M. (2006). Food protein-based materials as nutraceutical delivery systems. *Trends Food Sci Technol.*, **17**, 272–283.
- Church, M.W., Jen, K.-L.C., Jackson, D.A., Adams, B.R., Hotra, J.W. (2009). Abnormal neurological responses in young adult offspring caused by excess omega-3 fatty acid (fish oil) consumption by the mother during pregnancy and lactation. *Neurotoxicol Teratol.*, **31**, 26–33.
- Cohen, M. (1989). *Health and the rise of civilization*. Yale University Press; London.
- Cordain, L. (1999). Cereal grains: Humanity's double-edged sword. *World Review of Nutrition and Dietetics; Evolutionary aspects of nutrition and health: Diet, exercise, genetics and chronic disease*, 19–73.
- Cordain, L. (2002). The nutritional characteristics of a contemporary diet based upon Paleolithic food groups. *J Am Nutraceutical Assoc.*, **5**, 15–24.
- Cordain, L., Eades, M.R., Eades, M.D. (2003). Hyperinsulinemic diseases of civilization: more than just Syndrome X. *Comp Biochem Physiol A Mol Integr Physiol.*, **136**, 95–112.
- Cordain, L., Eaton, S.B., Miller, J.B., Lindeberg, S., Jensen, C. (2002a). An evolutionary analysis of the aetiology and pathogenesis of juvenile-onset myopia. *Acta Ophthalmol Scand.*, **80**, 125–135.
- Cordain, L., Eaton, S.B., Miller, J.B., Mann, N., Hill, K. (2002b). The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. *Eur J Clin Nutr.*, **56**, S42–S52.
- Cordain, L., Eaton, S.B., Sebastian, A., Mann, N., Lindeberg, S., Watkins, B.A., O'Keefe, J.H., Brand-Miller, J. (2005). Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr.*, **81**, 341–354.
- Cordain, L., Gotschall, R.W., Eaton, S.B., Eaton, S.B. (1998). Physical activity, energy expenditure and fitness: An evolutionary perspective. *Int J Sports Med.*, **19**, 328–335.
- Cordain, L., Lindeberg, S., Hurtado, M., Hill, K., Eaton, S.B., Brand-Miller, J. (2002c). Acne vulgaris – a disease of western civilization. *Arch Dermatol.*, **138**, 1584–1590.

- Cordain, L., Miller, J.B., Eaton, S.B., Mann, N., Holt, S.H.A., Speth, J.D. (2000). Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. *Am J Clin Nutr.*, **71**, 682–692.
- Cordain, L., Watkins, B.A., Florant, G.L., Kelher, M., Rogers, L., Li, Y. (2002d). Fatty acid analysis of wild ruminant tissues: evolutionary implications for reducing diet-related chronic disease. *Eur J Clin Nutr.*, **56**, 181–191.
- Crawford, M.A., Bloom, M., Broadhurst, C.L., Schmidt, W.F., Cunnane, S.C., Galli, C., Gehbremeskel, K., Linseisen, F., Lloyd-Smith, J., Parkington, J. (1999). Evidence for the unique function of docosahexaenoic acid during the evolution of the modern hominid brain. *Lipids*, **34**, S39–S47.
- Crawford, M.A., Broadhurst, C.L., Galli, C., Ghebremeskel, K., Holmsen, H., Saugstad, L.F., Schmidt, W.F., Sinclair, A.J., Cunnane, S.C. (2008). The role of docosahexaenoic and arachidonic acids as determinants of evolution and hominid brain development. In *Fisheries for Global Welfare and Environment, 5th World Fisheries Congress*, pp. 57–76.
- Crovetti, R., Porrini, M., Santangelo, A., Testolin, G. (1998). The influence of thermic effect of food on satiety. *Eur J Clin Nutr.*, **52**, 482–488.
- Cunnane, S.C. (2005). Origins and evolution of the Western diet: implications of iodine and seafood intakes for the human brain. *Am J Clin Nutr.*, **82**, 483–484.
- Cunnane, S.C. (2006). Survival of the fattest: the key to human brain evolution. *M-S (Med Sci)*, **22**, 659–663.
- Cunnane, S.C., Plourde, M., Stewart, K., Crawford, M.A. (2007). Docosahexaenoic acid and shore-based diets in hominin encephalization: a rebuttal. *Am J Hum Biol.*, **19**, 578–581.
- Damude, H.G., Kinney, A.J. (2008). Engineering oilseeds to produce nutritional fatty acids. *Physiol Plant*, **132**, 1–10.
- Danaei, G., Vander Hoorn, S., Lopez, A.D., Murray, C.J.L., Ezzati, M. (2005). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet*, **366**, 1784–1793.
- Das, U.N. (2006). Essential fatty acids: biochemistry, physiology and pathology. *Biotechnol J.*, **1**, 420–439.
- Das, U.N. (2008a). Beneficial actions of polyunsaturated fatty acids in cardiovascular diseases: but, how and why? *Current Nutr Food Sci.*, **4**, 2–31.
- Das, U.N. (2008b). Essential fatty acids and their metabolites could function as endogenous HMG-CoA reductase and ACE enzyme inhibitors, anti-arrhythmic, anti-hypertensive, anti-atherosclerotic, anti-inflammatory, cytoprotective, and cardioprotective molecules. *Lipids Health Dis.*, **7**, 37.
- de Groot, R.H., Hornstra, G., van Houwelingen, A.C., Roumen, F. (2004). Effect of alpha-linolenic acid supplementation during pregnancy on maternal and neonatal polyunsaturated fatty acid status and pregnancy outcome. *Am J Clin Nutr.*, **79**, 251–260.
- De Pinieux, G., Chariot, P., AmmiSaid, M., Louarn, F., Lejone, J.L., Astier, A., Jacotot, B., Gherardi, R. (1996). Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. *Br J Clin Pharmacol.*, **42**, 333–337.
- Delprato, S., Leonetti, E., Simonson, D.C., Sheehan, P., Matsuda, M., Defronzo, R.A. (1994). Effect of sustained physiological hyperinsulinemia and hyperglycemia on insulin-secretion and insulin sensitivity in man. *Diabetol.*, **37**, 1025–1035.
- Devine, A., Criddle, R.A., Dick, I.M., Kerr, D.A., Prince, R.L. (1995). A longitudinal-study of the effect of sodium and calcium intakes on regional bone-density in postmenopausal women. *Am J Clin Nutr.*, **62**, 740–745.
- Doyle, W., Crawford, M.A., Wynn, A.H.A., Wynn, S.W. (1989). Maternal nutrient intake and birth weight. *J Hum Nutr Diet.*, **2**, 407–414.
- Du, X.L., Edelstein, D., Dimmeler, S., Ju, Q., Sui, C., Brownlee, M. (2001). Hyperglycemia inhibits endothelial nitric oxide synthase activity by posttranslational modification at the Akt site. *J Clin Invest.*, **108**, 1341–1348.

- Duncan, R.E., El-Sohemy, A., Archer, M.C. (2005). Statins and cancer development. *Cancer Epidemiol Biomarkers Prev.*, **14**, 1897–1898.
- Duncan, R.E., El-Sohemy, A., Archer, M.C. (2006). Statins and the risk of cancer. *JAMA*, **295**, 2720.
- Duncan, R.E., El-Sohemy, A., Archer, M.C. (2007). Statins and cancer. *Epidemiology*, **18**, 520.
- Eaton, S.B.,d Konner, M. (1985). Paleolithic nutrition – a consideration of its nature and current implications. *N Engl J Med.*, **312**, 283–289.
- Eaton, S.B., Konner, M., Shostak, M. (1988). Stone agers in the fast lane – chronic degenerative diseases in evolutionary perspective. *Am J Med.*, **84**, 739–749.
- Engeset, D., Alsaker, E., Lund, E., Welch, A., Khaw, K.T., Clavel-Chapelon, F., Thiebaut, A., Chajes, V., Key, T.J., Allen, N.E. (2006). Fish consumption and breast cancer risk. The european prospective investigation into cancer and nutrition (EPIC). *Int J Cancer.*, **119**, 175–182.
- Farhang, B. (2007). Nanotechnology and lipids. *Lipid Technol.*, **19**, 132–135.
- First Data Bank (2000). *Nutritionist v nutrition software, version 2.3*. First Data Bank; San Bruno, CA.
- Frassetto, L., Morris, R.C., Sebastian, A. (1997). Potassium bicarbonate reduces urinary nitrogen excretion in postmenopausal women. *J Clin Endocrinol Metab.*, **82**, 254–259.
- Frassetto, L., Morris, R.C., Sellmeyer, D.E., Todd, K., Sebastian, A. (2001). Diet, evolution and aging – The pathophysiologic effects of the post-agricultural inversion of the potassium-to-sodium and base-to-chloride ratios in the human diet. *Eur J Nutr.*, **40**, 200–213.
- Frassetto, L.A., Todd, K.M., Morris, R.C., Sebastian, A. (1998). Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *Am J Clin Nutr.*, **68**, 576–583.
- Gago-Dominguez, M., Yuan, J.M., Sun, C.L., Lee, H.P., Yu, M.C. (2003). Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: the Singapore Chinese health study. *Br J Cancer*, **89**, 1686–1692.
- Gerrior, S., Bente, L. (2002). Nutrient content of the U.S. food supply, 1909–99: a summary report US Department of Agriculture, Home Economics report no. 55, Washington, DC.
- Gilani, G.S., Nasim, A. (2007). Impact of foods nutritionally enhanced through biotechnology in alleviating malnutrition in developing countries. *J AOAC Int.*, **90**, 1440–1444.
- Glenn, K.C. (2007). Nutritional and safety assessments of foods and feeds nutritionally improved through biotechnology: Lysine maize as a case study. *J AOAC Int.*, **90**, 1470–1479.
- Gotshall, R.W., Mickleborough, T.D., Cordain, L. (2000). Dietary salt restriction improves pulmonary function in exercise-induced asthma. *Med Sci Sports Exerc.*, **32**, 1815–1819.
- Graveland-Bikker, J.F., De Kruij, C.G. (2006). Unique milk protein based nanotubes: food and nanotechnology meet. *Trends Food Sci Technol.*, **17**, 196–203.
- Griffin, B.A. (2008). How relevant is the ratio of dietary n-6 to n-3 polyunsaturated fatty acids to cardiovascular disease risk? Evidence from the OPTILIP study. *Curr Opin Lipidol.*, **19**, 57–62.
- Harris, W.S., Poston, W.C., Haddock, C.K. (2007). Tissue n-3 and n-6 fatty acids and risk for coronary heart disease events. *Atherosclerosis*, **193**, 1–10.
- Hibbeln, J. (2002). Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J Affect Disord.*, **15**–29.
- Hibbeln, J., Davis, J., Steer, C., Emmett, P., Rogers, I., Williams, C., Golding, J. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet*, **369**, 578–585.
- Hibbeln, J., Nieminen, L., Lands, W. (2004). Increasing homicide rates and linoleic acid consumption among five Western countries, 1961–2000. *Lipids*, **39**, 1207–1213.

- Hibbeln, J.R., Nieminen, L.R.G., Blasbalg, T.L., Riggs, J.A., Lands, W.E.M. (2006). Healthy intakes of n-3 and n-6 fatty acids: estimations considering worldwide diversity. *Am J Clin Nutr.*, **83**, S1483–1493.
- Hirose, K., Takezaki, T., Hamajima, N., Miura, S., Tajima, K. (2003). Dietary factors protective against breast cancer in Japanese premenopausal and postmenopausal women. *Int J Cancer*, **107**, 276–282.
- Hooper, L., Thompson, R.L., Harrison, R.A., Summerbell, C.D., Ness, A.R., Moore, H.J., Worthington, H.V., Durrington, P.N., Higgins, J.P.T., Capps, N.E. (2006). Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *Br Med J.*, **332**, 752–760.
- House, S. (2000). Stages in reproduction particularly vulnerable to xenobiotic hazards and nutritional deficits. *Nutr Health*, **14**, 147–193.
- Innis, S.M. (2004). Polyunsaturated fatty acids in human milk: An essential role in infant development. *Adv Exp Med Biol.*, **554**, 27–43.
- Innis, S.M. (2005). Essential fatty acid transfer and fetal development. *Placenta*, **26**, 70–75.
- Innis, S.M. (2007). Fatty acids and early human development. *Early Hum Dev.*, **83**, 761–766.
- Institute of Medicine (2005). *Preventing childhood obesity: Health in the balance*. The National Academy Press; Washington DC.
- Institute of Medicine of the National Academies (2002). *Dietary fats: total fat and fatty acids*. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients) The National Academy Press; Washington, DC, pp. 335–432.
- Iribarren, C., Markovitz, J.H., Jacobs, D.R., Schreiner, P.J., Daviglus, M., Hibbeln, J.R. (2004). Dietary intake of n-3, n-6 fatty acids and fish: Relationship with hostility in young adults – the CARDIA study. *Eur J Clin Nutr.*, **58**, 24–31.
- Iso, H., Sato, S., Folsom, A.R., Shimamoto, T., Terao, A., Munger, R.G., Kitamura, A., Konishi, M., Iida, M., Komachi, Y. (1989). Serum Fatty Acids and Fish Intake in Rural Japanese, Urban Japanese, Japanese American and Caucasian American Men. *Int J Epidemiol.*, **18**, 374–381.
- Jansson, B. (1986). Geographic cancer risk and intracellular potassium-sodium ratios. *Cancer Detect Prev.*, **9**, 171–194.
- Johnston, C.S., Tjonn, S.L., Swan, P.D. (2004). High-protein, low-fat diets are effective for weight loss and favorably alter biomarkers in healthy adults. *J Nutr.*, **134**, 586–591.
- Joossens, J.V. and Geboers, J. (1981). Nutrition and gastric cancer. *Proc Nutr Soc.*, **40**, 37–46.
- Krauss, R.M., Eckel, R.H., Howard, B., Appel, L.J., Daniels, S.R., Deckelbaum, R.J., Erdman, J.W., Kris-Etherton, P., Goldberg, I.J., Kotchen, T.A., Lichtenstein, A.H., Mitch, W.E., Mullis, R., Robinson, K., Wylie-Rosett, J., Jeor, S.S., Suttie, J., Tribble, D.L., Bazzarre, T.L. (2000). AHA dietary guidelines – Revision 2000: A statement for healthcare professionals from the nutrition committee of the American Heart Association. *Circulation*, **102**, 2284–2299.
- Kris-Etherton, P.M., Harris, W.S., Appel, L.J. (2003). Omega-3 fatty acids and cardiovascular disease new recommendations from the American Heart Association. *Arterioscler Thromb Vasc Biol.*, **23**, 151–152.
- Kris-Etherton, P.M., Harris, W.S., Appel, L.J., Nutrition, C. (2002). Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*, **106**, 2747–2757.
- Lands, B. (2008). A critique of paradoxes in current advice on dietary lipids. *Prog Lipid Res.*, **47**, 77–106.
- Lands, W.E.M. (1986). *Fish and human health*. Academic Press Orlando, Fla.
- Lands, W.E.M. (1991). Biosynthesis of prostaglandins. *Annu Rev Nutr.*, **11**, 41–60.
- Lands, W.E.M. (2005). Dietary fat and health: the evidence and the politics of prevention – careful use of dietary fats can improve life and prevent disease. *Ann N Y Acad Sci.*, **1055**, 179–192.

- Lands, W.E.M., Libelt, B., Morris, A., Kramer, N.C., Prewitt, T.E., Bowen, P., Schmeisser, D., Davidson, M.H., Burns, J.H. (1992). Maintenance of lower proportions of (n-6) eicosanoid precursors in phospholipids of human plasma in response to added dietary (n-3) fatty-acids. *Biochim Biophys Acta*, **1180**, 147–162.
- Layman, D.K. (2003). The role of leucine in weight loss diets and glucose homeostasis. *J Nutr.*, **133**, 261S–267S.
- Ledikwe, J.H., Blanck, H.M., Kettel Khan, L., Serdula, M.K., Seymour, J.D., Tohill, B.C., Rolls, B.J. (2006). Dietary energy-density is associated with energy intake and weight status in US adults. *Am J Clin Nutr.*, **83**, 1362–1368.
- Libby, P. (2002). Atherosclerosis in inflammation. *Nature*, **420**, 868–874.
- Lichtenstein, A.H. (2005). Remarks on clinical data concerning dietary supplements that affect antithrombotic therapy. *Thromb Res.*, **117**, 71–73.
- Lindseth, G., Lindseth, P.D. (1995). The relationship of diet to airsickness. *Aviat Space Environ Med.*, **66**, 537–541.
- Liou, Y.A., King, D.J., Zibrik, D., Innis, S.M. (2007). Decreasing linoleic acid with constant (alpha)-linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. *J Nutr.*, **137**, 945.
- Litt, J., Taylor, H.G., Klein, N., Hack, M. (2005). Learning disabilities in children with very low birthweight: prevalence, neuropsychological correlates, and educational interventions. *J Learn Disabil.*, **38**, 130–141.
- Liu, S., Willett, W.C. (2002). Dietary glycemic load and atherothrombotic risk. *Curr Atheroscler Rep.*, **4**, 454–461.
- Lucca, P., Hurrell, R., Potrykus, I. (2002). Fighting iron deficiency anemia with iron-rich rice. *J Am Coll Nutr.*, **21**, 184S–190S.
- Ludwig, D.S. (2002). The glycemic index physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA*, **287**, 2414–2423.
- McLean, C.H., Newberry, S.J., Mojica, W.A., Khanna, P., Issa, A.M., Suttrop, M.J., Lim, Y.W., Traina, S.B., Hilton, L., Garland, R. (2006). Effects of omega-3 fatty acids on cancer risk a systematic review. *JAMA*, **295**, 403–415.
- Madden, S.G., Loeb, S.J., Smith, C.A. (2008). An integrative literature review of lifestyle interventions for the prevention of type II diabetes mellitus. *J Clin Nurs.*, **17**, 2243–2256.
- Marmot, M., Atinmo, T., Byers, T., Chen, J., Hirohata, T., Jackson, A., James, W.P.T., Kolonel, L.N., Kumanyika, S., Leitzmann, C. (2007). *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. American Institute for Cancer Research; Washington, DC.
- Massey, L.K., Whiting, S.J. (1995). Dietary salt, urinary calcium, and kidney-stone risk. *Nutr Rev.*, **53**, 131–134.
- McCarty, M.F. (2004). Should we restrict chloride rather than sodium? *Med Hypotheses*, **63**, 138–148.
- McClain, D.A. (2002). Hexosamines as mediators of nutrient sensing and regulation in diabetes. *J Diabetes Complicat.*, **16**, 72–80.
- McNamara, R.K., Carlson, S.E. (2006). Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins Leukot Essent Fatty Acids*, **75**, 329–349.
- Mickleborough, T.D., Gotshall, R.W., Kluka, E.M., Miller, C.W., Cordain, L. (2001). Dietary chloride as a possible determinant of the severity of exercise-induced asthma. *Eur J Appl Physiol.*, **85**, 450–456.
- Miller, M.M. (1945). Low sodium chloride intake in the treatment of insomnia and tension states. *JAMA*, **129**, 262.
- Morris, R.C., Sebastian, A., Forman, A., Tanaka, M., Schmidlin, O. (1999). Normotensive salt sensitivity – effects of race and dietary potassium. *Hypertension*, **33**, 18–23.
- Murray, C.J.L., Lopez, A.D. (1997). Alternative projections of mortality and disability by cause 1990–2020: Global burden of disease study. *Lancet*, **349**, 1498–1504.

- Nathan, C. (2008). Epidemic inflammation: pondering obesity. *Mol Med.*, **14**, 485–492.
- O'Keefe, S. (2000). *An overview of oils and fats, with a special emphasis on olive oil*. The Cambridge world history of food. (O.K. Kiple KF, Ed.) Cambridge University Press; United Kingdom, pp. 375–97.
- Obarzanek, E., Velletri, P.A., Cutler, J.A. (1996). Dietary protein and blood pressure. *JAMA*, **275**, 1598–1603.
- Odea, K. (1984). Marked improvement in carbohydrate and lipid-metabolism in diabetic australian aborigines after temporary reversion to traditional lifestyle. *Diabetes*, **33**, 596–603.
- Odea, K., Traianedes, K., Ireland, P., Niall, M., Sadler, J., Hopper, J., Deluise, M. (1989). The effects of diet differing in fat, carbohydrate, and fiber on carbohydrate and lipid-metabolism in type-II diabetes. *J Am Diet Assoc.*, **89**, 1076–1086.
- Ostman, E.M., Elmstahl, H., Bjorck, I.M.E. (2001). Inconsistency between glycemic and insulinemic responses to regular and fermented milk products. *Am J Clin Nutr.*, **74**, 96–100.
- Paine, J.A., Shipton, C.A., Chaggar, S., Howells, R.M., Kennedy, M.J., Vernon, G., Wright, S.Y., Hinchliffe, E., Adams, J.L., Silverstone, A.L. (2005). Improving the nutritional value of Golden Rice through increased pro-vitamin A content. *Nat Biotechnol.*, **23**, 482–487.
- Pak, C.Y.C., Fuller, C., Sakhaee, K., Preminger, G.M., Britton, F. (1985). Long-term treatment of calcium nephrolithiasis with potassium citrate. *J Urol.*, **134**, 11–19.
- Piatti, P.M., Monti, L.D., Magni, F., Fermo, I., Baruffaldi, L., Nasser, R., Santambrogio, G., Librenti, M.C., Gallikienle, M., Pontiroli, A.E., Pozza, G. (1994). Hypocaloric high-protein diet improves glucose-oxidation and spares lean body-mass – comparison to hypocaloric high-carbohydrate diet. *Metab Clin Exp.*, **43**, 1481–1487.
- Ponder, D.L., Innis, S.M., Benson, J.D., Siegman, J.S. (1992). Docosahexaenoic acid status of term infants fed breast milk or infant formula containing soy oil or corn oil. *Pediatr Res.*, **32**, 683–688.
- Porcelli, M.J., Gugelchuk, G.M. (1995). A trek to the top: a review of acute mountain sickness. *J Am Osteopath Assoc.*, **95**, 718–718.
- Preminger, G.M., Sakhaee, K., Skurla, C., Pak, C.Y.C. (1985). Prevention of recurrent calcium stone formation with potassium citrate therapy in patients with distal renal tubular-acidosis. *J Urol.*, **134**, 20–23.
- Reaven, G.M. (1995). Pathophysiology of insulin-resistance in human-disease. *Physiol Rev.*, **75**, 473–486.
- Rees, G., Doyle, W., Srivastava, A., Brooke, Z.M., Crawford, M.A., Costeloe, K.L. (2005). The nutrient intakes of mothers of low birth weight babies – a comparison of ethnic groups in East London, UK. *Matern Child Nutr.*, **1**, 91–99.
- Roberts, C.K., Barnard, R.J., Sindhu, R.K., Jurczak, M., Ehdaie, A., Vaziri, N.D. (2005). A high-fat, refined-carbohydrate diet induces endothelial dysfunction and oxidant/antioxidant imbalance and depresses NOS protein expression. *J Appl Physiol.*, **98**, 203–210.
- Roberts, C.K., Vaziri, N.D., Barnard, R.J. (2002). Effect of diet and exercise intervention on blood pressure, insulin, oxidative stress, and nitric oxide availability, Vol. 106, pp. 2530–2532. Am Heart Assoc.
- Robson, A. (2006). Shellfish view of omega-3 and sustainable fisheries. *Nature*, **444**, 1002.
- Rose, D.P., Connolly, J.M. (1999). Omega-3 fatty acids as cancer chemopreventive agents. *Pharmacol Ther.*, **83**, 217–244.
- Ross, R. (1999). Atherosclerosis – an inflammatory disease. *N Engl J Med.*, **340**, 115–126.
- Rossetti, L., Giaccari, A., Defronzo, R.A. (1990). Glucose toxicity. *Diabetes Care*, **13**, 610–630.
- Russo, G.L. (2009). Dietary n-6 and n-3 polyunsaturated fatty acids: From biochemistry to clinical implications in cardiovascular prevention. *Biochem Pharmacol.*, **77**, 937–946.



- Ruxton, C.H.S., Reed, S.C., Simpson, M.J.A., Millington, K.J. (2004). The health benefits of omega-3 polyunsaturated fatty acids: a review of the evidence. *J Hum Nutr Diet.*, **17**, 449–459.
- Salem, N., Litman, B., Kim, H.Y., Gawrisch, K. (2001). Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids*, **36**, 945–959.
- Samuelsson, B. (1979). Prostaglandins, thromboxanes, and leukotrienes: formation and biological roles. *Harvey Lect.*, **75**, 1–40.
- Schaefer, O. (1971). When the Eskimo comes to town. *Nutr Today*, **6**, 8–16.
- Schumacher, M.C., Laven, B., Wolk, A., Brendler, C.B., Ekman, P. (2007). Do omega-3 dietary fatty acids lower prostate cancer risk? A review of the literature. *Curr Urol.*, **1**, 2–10.
- Scientific Advisory Committee on Nutrition (SACN) (2004). Advice on fish consumption: benefits and risks. The Stationery Office; Norwich.
- Sebastian, A., Frassetto, L.A., Sellmeyer, D.E., Merriam, R.L., Morris, R.C. (2002). Estimation of the net acid load of the diet of ancestral preagricultural *Homo sapiens* and their hominid ancestors. *Am J Clin Nutr.*, **76**, 1308–1316.
- Sebastian, A., Harris, S.T., Ottaway, J.H., Todd, K.M., Morris, R.C. (1994). Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med.*, **330**, 1776–1781.
- Seino, Y., Seino, S., Ikeda, M., Matsukura, S., Imura, H. (1983). Beneficial-effects of high protein-diet in treatment of mild diabetes. *Hum Nutr Appl Nutr.*, **37**, 226–230.
- Sharma, A.M., Kribben, A., Schattenfroh, S., Cetto, C., Distler, A. (1990). Salt sensitivity in humans is associated with abnormal acid-base regulation. *Hypertension*, **16**, 407–413.
- Silvers, K., Woolley, C., Hamilton, F., Watts, P., Watson, R. (2005). Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression *Prostaglandins Leukot Essent Fatty Acids*, **72**, 211–218.
- Sinclair, H.M. (1956). Deficiency of essential fatty acids and atherosclerosis, etcetera. *Lancet*, **270**, 381–383.
- Siritunga, D., Sayre, R.T. (2003). Generation of cyanogen-free transgenic cassava. *Planta*, **217**, 367–373.
- Skov, A.R., Toubro, S., Ronn, B., Holm, L., Astrup, A. (1999). Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. *Int J Obes.*, **23**, 528–536.
- Sorrentino, A., Gorrasi, G., Vittoria, V. (2007). Potential perspectives of bio-nanocomposites for food packaging applications. *Trends Food Sci Technol.*, **18**, 84–95.
- Sozer, N., Kokini, J.L. (2009). Nanotechnology and its applications in the food sector. *Trends Biotechnol.*, **27**, 82–89.
- Stoll, A.L., Damico, K.E., Daly, B.P., Severus, W.E., Marangell, L.B. (2001). Methodological considerations in clinical studies of omega 3 fatty acids in major depression and bipolar disorder. *Fatty Acids And Lipids – New Findings*, **88**, 58–67.
- Stoll, G., Bendszus, M. (2006). Inflammation and atherosclerosis: novel insights into plaque formation and destabilization. *Stroke*, **37**, 1923–1932.
- Stubbs, R.J. (1998). Appetite, feeding behaviour and energy balance in human subjects. *Proc Nutr Soc.*, **57**, 341–356.
- Terry, P.D., Terry, J.B., Rohan, T.E. (2004). Long-chain (n-3) fatty acid intake and risk of cancers of the breast and the prostate: recent epidemiological studies, biological mechanisms, and directions for future research. *J Nutr.*, **134**, 3412–3420.
- Thai-Van, H., Bounaïx, M.J., Frayssé, B. (2001). Meniere's disease: pathophysiology and treatment. *Drugs*, **61**, 1089–1102.
- Thiebaut, A.C.M., Chajes, V., Gerber, M., Boutron-Ruault, M.-C., Joulin, V., Lenoir, G., Berrino, F., Riboli, E., Benichou, J., Clavel-Chapelon, F. (2009). Dietary intakes of omega-6 and omega-3 polyunsaturated fatty acids and the risk of breast cancer. *Int J Cancer*, **124**, 924–931.

- Thomson, M.J., Williams, M.G., Frost, S.C. (1997). Development of insulin resistance in 3T3-L1 adipocytes. *J Biol Chem.*, **272**, 7759–7764.
- Tolfree, D., Smith, A. (2009). *Roadmapping emergent technologies*. Leicester: Matador.
- Trowell, H. (1985). Dietary fibre: a paradigm. In *Dietary fibre, fibre-depleted foods and disease* (H.C. Trowell, D. Burkitt and K.W. Heaton, eds), pp. 1–20. Academic Press; London.
- Trowell, H.C. (1980). From normotension to hypertension in Kenyans and Ugandans 1928–1978. *East Afr Med J.*, **57**, 167–173.
- Truswell, A.S. (1977). *Diet and nutrition of hunter-gatherers. Health and disease in tribal societies*. New York: Elsevier.
- Turner, R., McLean, C.H., Silvers, K.M. (2006). Are the health benefits of fish oils limited by products of oxidation? *Nutr Res Rev.*, **19**, 53–62.
- Tuyns, A.J. (1988). Salt and gastrointestinal cancer. *Nutr Cancer*, **11**, 229–232.
- U.S. Department of Agriculture (2008). Nutrient intakes from food: Mean amounts consumed per individual, one day, 2005–2006. Agricultural Research Service [www.ars.usda.gov/ba/bhnrc/fsrg](http://www.ars.usda.gov/ba/bhnrc/fsrg).
- Vasconcelos, M., Datta, K., Oliva, N., Khalekuzzaman, M., Torrizo, L., Krishnan, S., Oliveira, M., Goto, F., Datta, S.K. (2003). Enhanced iron and zinc accumulation in transgenic rice with the ferritin gene. *Plant Sci.*, **164**, 371–378.
- von Schacky, C., Harris, W.S. (2007). Cardiovascular benefits of omega-3 fatty acids. *Cardiovasc Res.*, **73**, 310–315.
- Wakai, K., Tamakoshi, K., Date, C., Fukui, M., Suzuki, S., Lin, Y., Niwa, Y., Nishio, K., Yatsuya, H., Kondo, T., Tokudome, S., Yamamoto, A. (2005). Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. *Cancer Sci.*, **96**, 590–599.
- Wathes, D.C., Abayasekara, D.R.E., Aitken, R.J. (2007). Polyunsaturated fatty acids in male and female reproduction. *Biol Reprod.*, **77**, 190–201.
- Westertep-Plantenga, M.S., Lejeune, M., Nijs, I., van Ooijen, M., Kovacs, E.M.R. (2004). High protein intake sustains weight maintenance after body weight loss in humans. *Int J Obes.*, **28**, 57–64.
- Whitaker, J.W. (1975). *Feedlot empire: beef cattle feeding in Illinois and Iowa 1840–1900*. Iowa State University Press.
- Willatts, P., Forsyth, J.S. (2000). The role of long-chain polyunsaturated fatty acids in infant cognitive development. *Prostaglandins, Leukotrienes & Essential Fatty Acids*, **63**, 95–100.
- Williams, G.C., Nesse, R.M. (1994). *Why we get sick: the new science of Darwinian medicine*. New York: Times Books.
- Wolfe, B.M., Giovannetti, P.M. (1991). Short-term effects of substituting protein for carbohydrate in the diets of moderately hypercholesterolemic human-subjects. *Metab Clin Exp.*, **40**, 338–343.
- Wolfe, B.M., Giovannetti, P.M. (1992). High protein-diet complements resin therapy of familial hypercholesterolemia. *Clin Investig Med.*, **15**, 349–359.
- Wolfe, B.M.J., Piche, L.A. (1999). Replacement of carbohydrate by protein in a conventional-fat diet reduces cholesterol and triglyceride concentrations in healthy normolipidemic subjects. *Clinical Investig Med. – Medecine Clinique Et Experimentale*, **22**, 140–148.
- World Health Organization (2005a). *Modern food biotechnology, human health and development: an evidence-based study*. World Health Organization Geneva, Switzerland.
- World Health Organization (2009a). Composition of World health expenditures [http://www.who.int/nha/Pie\\_chart\\_2006.pdf](http://www.who.int/nha/Pie_chart_2006.pdf).
- World Health Organization (2006). Obesity and overweight. Fact sheet N°311.
- World Health Organization (2007). Cardiovascular diseases. Fact sheet N°317.
- World Health Organization (2008a). Cancer. Fact sheet N°297.
- World Health Organization (2008b). Diabetes. Fact sheet N°312.





- World Health Organization (2009b). Micronutrient deficiencies: Iron deficiency anaemia <http://www.who.int/nutrition/topics/ida/en/print.html>.
- Wynn, S.W., Wynn, A.H.A., Doyle, W., Crawford, M.A. (1994). The association of maternal social class with maternal diet and the dimensions of babies in a population of London Women. *Nutr Health*, **9**, 303–315.
- Zammit, V.A., Waterman, I.J., Topping, D., McKay, G. (2001). Insulin stimulation of hepatic triacylglycerol secretion and the etiology of insulin resistance. *J Nutr.*, **131**, 2074–2077.
- Zieske, A.W., Malcom, G.T., Strong, J.P. (2002). Natural history and risk factors of atherosclerosis in children and youth: the pday study. *Pediatr Pathol Mol Med.*, **21**, 213–237.